Protecting Participants and Their Communities

The Tissue Issue: Ethical and Legal Issues in Biorepository Research

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Agenda

- Informed consent
- Withdrawal of consent
- Right to receive results of study
- Participant privacy
- American Indian participants and their communities

Informed Consent

The Elements of Consent

- 45 CFR 46.116 has the general rules while 46.117 has the documentation rules
- The elements of consent are:

  1. A competent non-coerced subject with sufficient opportunity to understand the proposed research and decide whether or not to participate

The Elements of Consent

2. No exculpatory language, i.e.,
   "You waive any rights you have to commercial profit from this research"
   vs.
   "No payment is available for this research or any commercial developments."
3. The research, its potential benefits, foreseeable risks and alternatives

The Elements of Consent

4. Will confidentiality be maintained? How?
5. Is there any compensation?
6. Who can be contacted for answers?
7. Participation is voluntary and can be discontinued at any time

   Q: What if tissue identifiers have been removed?

The Elements of Consent

8. Will “significant new findings” be provided to the patient?
9. What are the consequences if subject decides to withdraw?
10. The decision to participate or not will not result in any penalty or loss of subject’s otherwise entitled to benefits

Risks to the Participant

- Obtaining the tissue is usually only minimal physical risk
- The issue is how to discuss social risks: potential for loss of insurance, loss of job, loss of confidentiality (even though there may be legal remedies for improper disclosure or improper use)

Risk to the Subject from Disclosure of Genetic Information

- Impact on insurability
- Impact on employability
- Impact on sense of self
  - Social esteem
  - Deviation from “normal”
- Impact on future health risk
  - Can research findings be trusted?
  - Should research information guide clinical decision-making?

Risk to the Family from Disclosure of Genetic Information

- Previously undisclosed paternity or parentage
- Social esteem
- Anxiety about familial deviation from “normal”
- Survivor guilt
- Family secrets…

How to Discuss Risks?

- Example: “Although we take pains to protect your privacy a tissue analysis may find its way into your medical record which may later be disclosed by you to a life insurance company which may then deny or increase the cost of insurance based on research test results.”

Tiered Consent

- Informed Consent Alternatives:
  1. No research use permitted
  2. Only anonymous research use
  3. Project specific use, no further contact
  4. Project specific use, contact for future use
  5. Project specific and related project use
  6. Project specific and other study use (allowable?)
  7. Commercial use

Banked Tissue Information

Date of Collection:	5/2/02
Pt. Name &/or Spec. #	3228
Sample Type:	Lung Biopsy Spec.
Consent obtained?	Yes
■ **Only for this study**	No
■ **For related studies**	Yes
■ **For any study**	No
Recontact allowed	Yes

Commercial Sponsor Push-Back

- What if the commercial sponsor for your research says that it wants to collect as many samples as possible with no tiered consent, and at the end of your study you will be required to send all samples to the sponsor? The sponsor will add the samples to its data base.

Tissue Collection from Minors

- Is assent required?
- What happens when subject turns 18?
  - Recontact and consent required?
  - What if whereabouts unknown?
  - What do you do now?
    - Throw away specimen
    - Anonymize specimen
    - Hire a private detective

Other Potential Problem Areas

- Anonymous versus linked samples
- Will research info find its way into the medical record?
- Sharing with other researchers
- Future use for other studies
  - Secondary use, or unclear use
  - DNA banking (implied promises)
- Withdrawal from study
- Study termination

Does Consent Matter?

- If the process of informed choice is carefully observed two things should happen:
  1. You have, and can document, that the rules were followed; and
  2. You have created a supportive relationship between you and the subject with mutual trust and respect

Does Consent Matter?

- What if subjects say that they don't care about "left-over" tissue and want it to be used for "good research"?
- Is consent for tissue different from consent for invasive research? Why? What is different about the risks?
- Do subjects really understand?

Consent Example #1

- I want your DNA to study Alzheimer's Disease. Your sample will not be identifiable. You will not get any results back. Anything I learn I will publish. Perhaps this will generate new knowledge from which you will benefit in the future. Do you want to participate?

Consent Example #2

- I want your DNA for the above described research, but I will keep your sample and in 5 years I may do some other not yet determined research. I will not re-contact you. Do you consent to participate?
- Should the IRB impose limits on the autonomy to consent?

Waiver of Informed Consent

Waiver of Consent

- IRB may waive elements of consent, or the entire consent
  - No more than minimal risk
  - Waiver will not adversely affect the rights and welfare of subjects
    - Consider the magnitude of the psychosocial risks and the likelihood that research results will be reported to the subject or to third parties
  - Research could not practicably be conducted without the waiver
  - Whenever appropriate, subjects will be provided with additional pertinent information

(Emanuel, Crouch, Arras, Moreno, & Grady, 2003)

Waiver of Consent

- In determining whether informed consent subjects who donated samples is impracticable:
  - Consent cannot be waived on the simple assertion that seeking it would be tedious, burdensome, or costly

    (Emanuel, Crouch, Arras, Moreno, & Grady, 2003)

If consent is required…

- Review original consent forms to evaluate whether the new research conforms with or goes beyond the provisions of the original consent
- Check to see if the original consent form includes a statement about recontact of subjects and the circumstances under which this would or would not occur

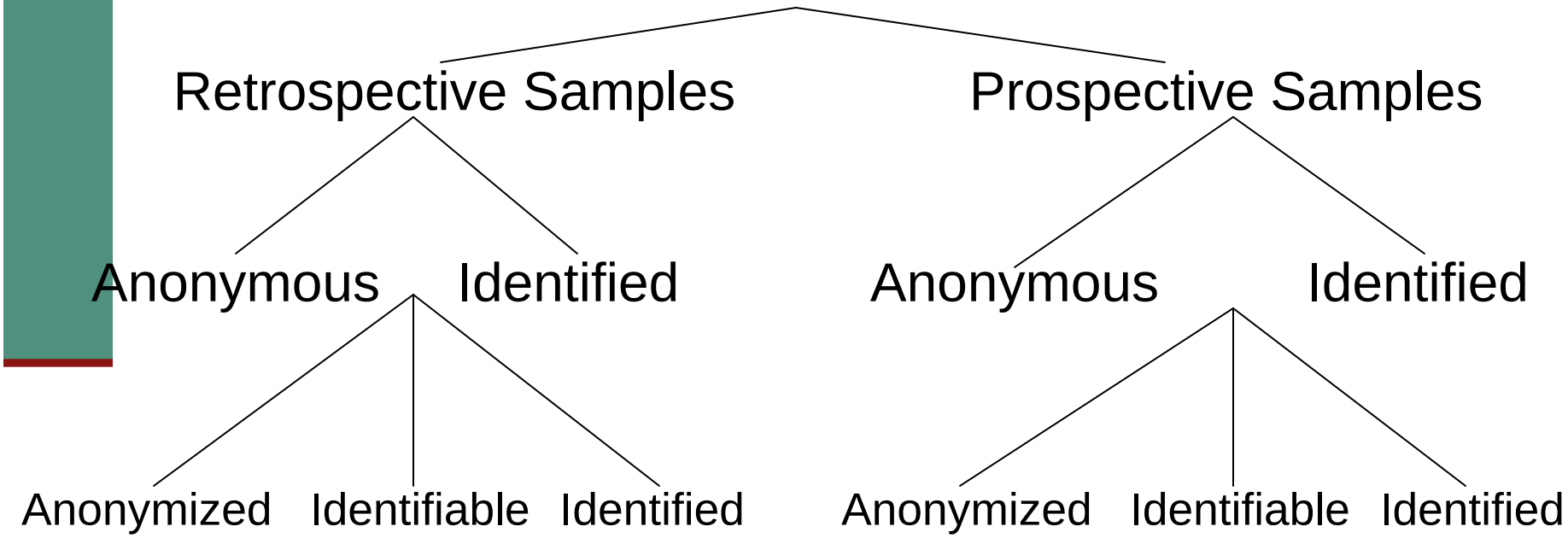
(Emanuel, Crouch, Arras, Moreno, & Grady, 2003)

Waiver of informed consent for "anonymized" samples

- Discussions concerning research using stored biological samples have been confusing due to vague terms – American Society of Human Genetics (ASHG) describes four types of biological samples under two broad classes of such samples

  (Emanuel, Crouch, Arras, Moreno, & Grady, 2003)

Classification of Samples



(Emanuel, Crouch, Arras, Moreno, & Grady, 2003)

Why use anonymized samples?

- Benefits to using retrospectively obtained samples which are anonymous/ anonymized
- Reduction of risks to subjects
- Eliminates the requirement to reconsent subjects (eliminates bias related to those whom you are unable to contact and those who do not wish to reconsent)

(Emanuel, Crouch, Arras, Moreno, & Grady, 2003)

Withdrawal of Consent

Withdrawal of Consent

- Subjects should be informed regarding withdrawal of their samples and under what circumstances this withdrawal can occur
- Anonymized samples cannot be withdrawn (if this is to occur, inform the subject when so that samples can be withdrawn up to that point)

(Emanuel, Crouch, Arras, Moreno, & Grady, 2003

Disposition of Samples

- Subjects should be informed if samples will be destroyed or stored for future use

  (Emanuel, Crouch, Arras, Moreno, & Grady, 2003)

Communication of Results

Results of Research Provided to Participant

- Subjects may be given the opportunity to receive information regarding the results of tests performed as part of the research
- Participants may have access to research results before the meaning and utility of results are proven
- If information will not be shared, subjects must be made aware of this fact during consent

(Emanuel, Crouch, Arras, Moreno, & Grady, 2003)

Results of Research Provided to Participant

- *General* results can be given to subjects
- Researchers should carefully consider how the findings are written
  - Present findings with an understanding of the study community's circumstances (may be difficult when the values and social conditions of the study community are radically different from that of the outside reading audience)

(Dunn and Chadwick, 2002

Results of Research Provided to Participant

- Genetic research in which identifiable or identified samples will be used and disclosure of results is planned should have medical geneticists or genetic counselors as part of research personnel so that results are communicated accurately and appropriately

(Emanuel, Crouch, Arras, Moreno, & Grady, 2003)

Results of Research Provided to Participant

- Disclosure of results generally should be based on the following considerations:
  - Magnitude of the threat posed
  - Accuracy with which the data can predict the threat
  - Potential that there will be an intervention to treat the threat

  (Emanuel, Crouch, Arras, Moreno, & Grady, 2003)

Results of Research Provided to Participant

- Study communities may want to review written accounts and be allowed to comment prior to publication or presentation
- This will often prevent publication of sensitive, embarrassing, or divisive information

  (Dunn and Chadwick, 2002)

Results of Research Provided to Participant

- The right "not to know":
  - Unaware of the incidence of a disease in their family
  - Have not sought information concerning their own risk of developing the disease
  - Deny that the disease is an issue for them

  (Emanuel, Crouch, Arras, Moreno, & Grady, 2003)

Results of Research Provided to Participant

Patient access to research results

Autonomy Centered	Beneficence Centered
■ Participants should always be given results and they can then do what they wish with the information	■ Participants should be given results when the data are validated and clinical utility is established

Results of Research Provided to Family

- Results or samples should not be provided to family members without the written permission of the subject
  - Privacy concerns(family secrets are revealed such as adoption, incest, artificial insemination, or nonpaternity)
  - Disclosure of a familial disease (may be disclosed during the recruitment process)

  (Emanuel, Crouch, Arras, Moreno, & Grady, 2003)

Participant Privacy

HIPAA Basics

- The HIPAA research rules apply anytime a HIPAA "covered entity" internally accesses or externally discloses protected health information (PHI) of a patient or a patient's family members, household members, or employers
- PHI includes any information containing HIPAA "identifiers"

HIPAA "Identifiers"

- Name;
- Street address, city, county, precinct, or zip code (unless only the first three digits of the zip code are used and the area has more than 20,000 residents);
- **The month and day of dates directly related to an individual, such as birth date, admission date, discharge date, dates of service, or date of death**;
- Age if over 89 (unless aggregated into a single category of age 90 and older);
- Telephone numbers;
- Fax numbers;
- Email addresses;
- Social security numbers;
- Medical record numbers;
- Health plan beneficiary numbers;
- Account numbers;
- Certificate/license numbers;
- Vehicle identifiers, serial numbers, and license plate numbers;
- Device identifiers and serial numbers;
- Web Universal Resource Locators (URLs) and Internet Protocol (IP) addresses;
- Biometric identifiers, such as fingerprints
- Full-face photographs and any comparable images; or
- Any other unique identifying number, characteristic, or code.

HIPAA Basics

- HIPAA often applies to three separate stages in tissue research:
  - (1) the collection and processing of samples from the participants (fully-identifiable patient information generally is used for that curation process);
  - (2) release of the samples to the researcher, if limited HIPAA identifiers will be included with the samples (particularly dates of service and dates of tissue collection); and
  - (3) use for the research, if the research is conducted by a HIPAA covered entity
- Nine HIPAA "options" are available to use or disclose PHI for research — you must meet the requirements of only <u>one</u> option

HIPAA Research Option #1

De-Identify PHI

- Ways to de-identify under HIPAA:
  - Remove identifiers (unless you know that even without identifiers, the information could be used to identify the individual)
  - Document that there is a statistically "very small" risk that information could be used to identify (even though identifiers are included)
  - Code identifiers (but code cannot be derived from patient identifiers)
- Biospecimen is not "PHI" unless it is correlated with HIPAA identifiers

Common Rule Coding

- Biospecimen is not identifiable if:
  - Destroy key to code before research begins;
  - Investigators and holder of key enter into agreement prohibiting release of key to investigators until individuals are deceased;
  - Have IRB approve written policies and procedures for a repository or data management center that prohibit the release of the key to investigators until individuals deceased; or
  - Determine that other legal requirements exist that prohibit release of key to investigators

FDA De-identification

- FDA generally requires informed consent and does not permit the use of de-identified biospecimens for FDA-regulated research unless:
  - *In-vitro* diagnostic device study that meets the IDE exemption criteria
  - Study uses leftover specimens collected for clinical purposes or specimens in a repository
  - Specimens cannot be individually identifiable to investigator, sponsor or any individual associated with the study (but the specimen may be coded and accompanied by de-identified clinical information)
  - Individuals caring for patients must be different from those conducting study
  - Supplier must have policy that prevents release of identifiable information
  - Study protocol must be reviewed by an IRB

To meet all three standards:

- Remove all HIPAA identifiers; or
- Get a statistical opinion that the biospecimens are not identifiable; or
- Code the biospecimens:
  - Code may not be derived from any patient HIPAA identifier (medical record number, social security number, etc.); and
  - An agreement, policy or legal requirement prohibits release to investigator before death of patient; and
  - Person involved in study cannot hold link

HIPAA Research Option #2

Use a Limited Data Set

- Partially de-identify PHI: remove all identifiers except dates related to individual (dates of service), geographic designations (above street level), and other identifiers not expressly listed in regulations
- Must have "data use agreement" in place with recipient

Application to Biospecimens

- Biospecimen studies typically ask for dates of service, diagnosis, collection, etc. (all HIPAA identifiers)
- If these are included, is a limited data set (but is not de-identified under HIPAA)

HIPAA Research Option #3

Obtain subject authorization

- HIPAA requires numerous elements—see template HIPAA authorization
- Do not combine HIPAA authorization with informed consent in biorepository research
  - HIPAA authorization may not seek permission to use or disclose PHI for future unspecified research—authorization must be protocol specific or must be for storage only

Don't combine authorizations for repository and clinical trial

- May require participant to sign authorization to use or disclose PHI for clinical trial, as condition of participating in trial
- Cannot require participant to sign authorization to collect PHI for storage in repository (if PHI will be used beyond the particular clinical trial)
- Cannot combine these authorizations (into a "compound authorization") where subject receiving treatment in a clinical trial
- Options:
  - Have separate authorization forms for particular clinical trial and collection of PHI for repository; or
  - Make clear that participant does not have to agree to portion that authorizes collection of PHI for repository

HIPAA Research Option #4

Have IRB waive or alter the need for an authorization

- Use or disclosure of PHI involves no more than minimal risk to their privacy, based on: (a) an adequate plan to protect PHI from improper use and disclosure; (b) an adequate plan to destroy PHI at the earliest opportunity consistent with conduct of the research (unless there is a health or research justification for retention or if retention is required by law); and (c) adequate written assurances that the PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the study, or for other research permitted by the rules.

HIPAA Research Option #4

Have IRB waive or alter the need for an authorization

- The research could not practicably be conducted without the waiver or alteration of authorization; and
- The research could not practicably be conducted without access to and use of information identifying the subjects

HIPAA Research Option #5

Obtain representations that PHI is for activities to prepare for research

- PHI solely to prepare for research, PHI necessary for research, and PHI will not be removed from premises
- But watch the Common Rule here—access to PHI to prepare for research requires IRB review unless exempt

HIPAA Research Option #6

Obtain representations regarding research involving decedents

- Researcher only seeks decedents' PHI, PHI necessary for the research, and documentation of death at request of covered entity
- Common Rule doesn't apply to decedents' information

HIPAA Research Option #7

Disclosure is required by law

- Example: Disclosure to OHRP or FDA during an investigation or compliance review

HIPAA Research Option #8

Patient Recruitment

- Contact of own patients for participation is "treatment" or "health care operations"
- Can have non-employed third party contact patients (including investigator) if business associate agreement in place with the third party
- Can ask IRB to partially waive HIPAA authorization for recruitment

HIPAA Research Option #9

Research is "grandfathered"

- If informed consent signed, or if the IRB waived informed consent, before April 14, 2003, may continue to collect, use and disclose PHI
  - Does not apply to patients enrolled after this date
  - Does not apply if informed consent document amended

HIPAA Usually Doesn't Apply After Disclosure of PHI

- HIPAA Privacy Rule does not prohibit use for secondary research by non-covered entities: Authorization informs subjects that once disclosed, PHI may not be protected by HIPAA
- Secondary research must comply with scope of the informed consent document– what type of protection should IRBs require?

Common Rule Requirements

- For "human subject research" IRB must determine that there are adequate provisions to protect the privacy of subjects and to maintain data confidentiality (45 CFR 46.111)
  - IRB Guidebook, Chapter 3D at http://www.hhs.gov/ohrp/irb/irb_chapter3.htm

Certificates of Confidentiality

- Certificates of Confidentiality available from NIH for "sensitive" research information where disclosure of identifying information could damage subjects' financial standing, employability, insurability or reputation
  - Research collecting information related to genetics, psychological well being, sexual behavior, drug use, criminal activities
  - Research where subjects may be involved in litigation related to exposures under study